Exhibit F

Idiopathic Intracranial Hypertension

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Idiopathic intracranial hypertension is a secondary headache disorder characterized by headaches and visual symptoms. It most frequently occurs in obese women of childbearing age. However, many secondary causes exist, and it may affect children, men, and slim individuals. Prompt recognition, evaluation, and treatment are needed to prevent permanent visual loss.

Introduction

Idiopathic intracranial hypertension (IIH) is diagnosed when the following conditions are met: 1) symptoms and signs, if present, representing only those of intracranial hypertension or papilledema; 2) normal neuroimaging studies; 3) increased cerebrospinal fluid (CSF) pressure with normal CSF contents; 4) normal mental status; and 5) no other cause is identified [1]. When an underlying cause is found, the clinical syndrome is termed "pseudotumor cerebri" or "intracranial hypertension from a secondary cause." IIH generally occurs in patients aged younger than 50 years and most commonly affects obese women of childbearing age. The incidence of IIH in the United States has increased over the past 15 years, possibly attributed to heightened awareness of the disorder or the increasing prevalence of obesity. Current estimates place the incidence of IIH between 2 and 5.2 per 100,000 in the general population, affecting approximately 20/100,000 obese women aged between 20 and 44 years [2,3]. Although it was initially described over 100 years ago, there is still significant controversy surrounding the management IIH, due to the paucity of prospective studies and lack of controlled treatment trials. Moreover, the pathophysiology of IIH is not understood. Regardless, prompt diagnosis and treatment are needed to prevent permanent visual loss.

Symptoms and Signs of IIH

Headache is the most common presenting symptom of IIH, experienced by more than 90% of patients [4,5]. IIH may be a cause of new daily persistent headache and should be suspected in patients with recent onset of progressively worsening, disabling headaches. The headache is most frequently described as retro-ocular, frontal, and pressure-like, but it varies considerably [6]. There may be migrainous features with throbbing, photophobia, phonophobia, and nausea. The pain may be worse upon awakening and is frequently described as the worst headache of one's life. Transient visual obscurations occur in approximately 75% of patients. They may be uniocular or binocular, consisting of partial or complete visual loss that is often provoked by a change in posture. The visual obscurations usually last less than 60 seconds and reflect papilledema. Approximately 50% of IIH patients have pulsatile tinnitus that is often not volunteered and must be specifically queried. Binocular diplopia, blurred vision, and subjective visual field loss may be present. Less common symptoms include ataxia, vertigo, disturbed hearing, torticollis, and facial palsy [7]. Neck, back, or radicular pain is sometimes prominent. Fever, meningismus, an altered sensorium, or focal neurologic deficits suggest another diagnosis.

The hallmark of IIH is papilledema, which is usually bilateral but may be asymmetric or unilateral [8]. The timing of papilledema in relation to the patient's symptoms is uncertain. Papilledema may be present early in the course; some experts maintain that it develops before the patient becomes symptomatic. It is not known whether it must evolve over days to weeks or whether the optic nerves may become visibly swollen in a shorter time period. Thirty-seven patients who were admitted to a neurosurgical intensive care unit with acute intracranial hypertension from cerebral hemorrhage of trauma were examined daily, using direct and indirect ophthalmoscopy [9]. All patients underwent continuous intracranial pressure monitoring. Only one patient had papilledema acutely. At 1 week, venous congestion developed in two patients with mild intracranial hypertension, but no other patients had papilledema. Thus, papilledema may lag behind acute increases of intracranial pressure in some circumstances.

Features of papilledema that correlate with the severity of IIH include obscuration of the major vessels coursing over the disc margin, disc elevation, loss of the physiologic cup, and a peripapillary halo [10]. Hemorrhages, exudates, retinal infarcts, choroidal folds, and macular edema also may be present (Fig. 1). Papilledema may be difficult to detect using a direct ophthalmoscope,

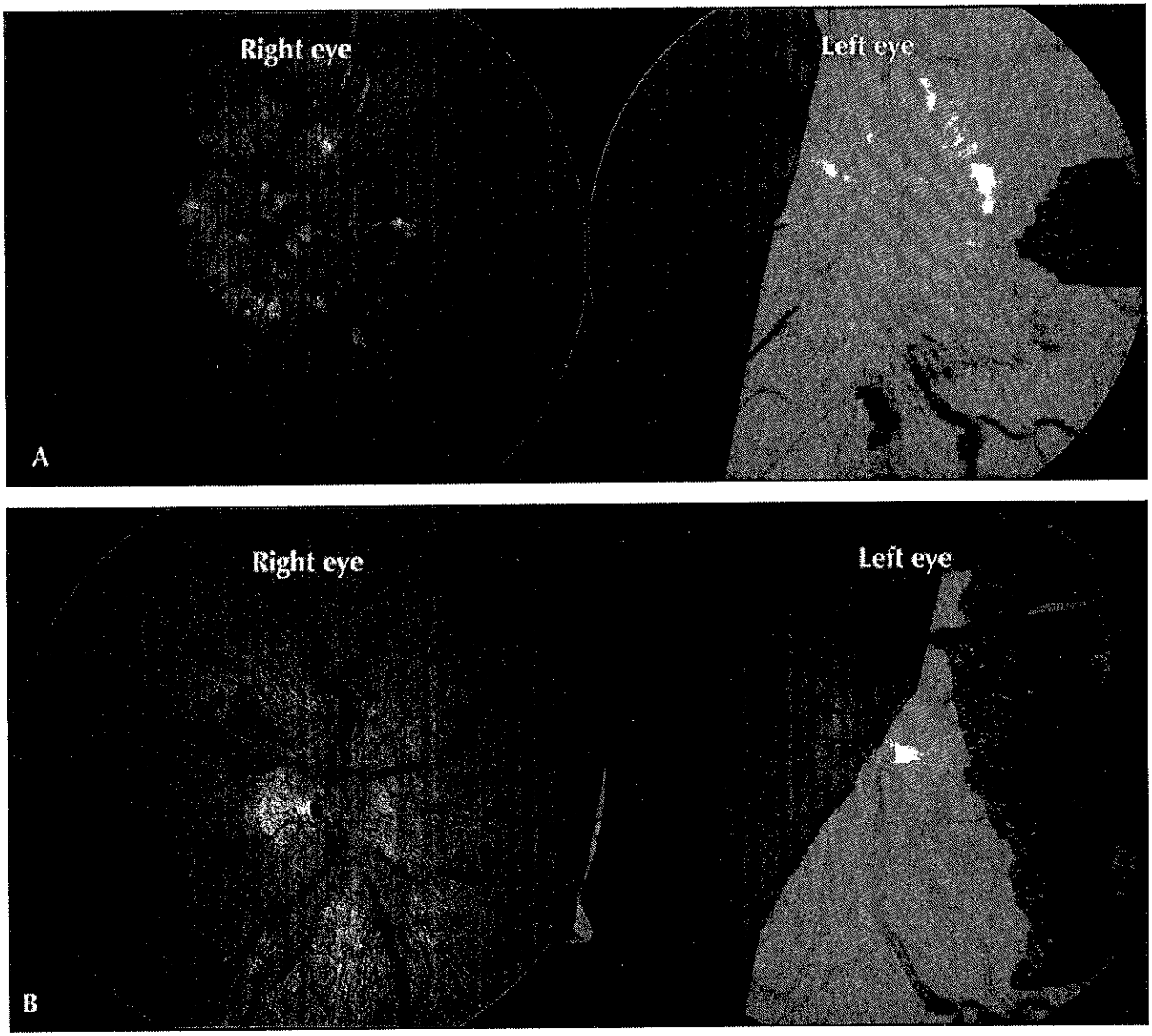

Figure 1. A, Bilateral papilledema in a 31-year-old woman with back and neck pain, severe throbbing headaches, phonophobia, and photophobia and diplopia. Visual acuity was 20/20 OD and 20/80 OS. Lumbar puncture showed an opening pressure of 510 mm cerebrospinal fluid. **B**, Optic nerves. Two weeks later, after treatment with acetazolamide, repeated lumbar punctures, and a lumboperitoneal shunt, there is marked improvement in her visual acuity (20/25 OU) and optic disc swelling. OD—right eye; OS—left eye; OU—both eyes.

and an ophthalmologic consultation is recommended. Stereoscopic viewing of the optic disc also is useful to distinguish true papilledema from pseudopapilledema caused by anomalous discs, tiled optic nerves, or optic disc drusen. Once optic atrophy is present, papilledema cannot be used to assess the intracranial pressure status.

Central vision is usually impaired late in the course of papilledema, but the visual field is involved early. Early visual field defects include enlargement of the physiologic blind spot, inferonasal loss, and generalized constriction of the visual field (Fig. 2) [11]. Visual field constriction from IIH must be differentiated from nonorganic visual field constriction, which may be coexistent. Quantitative perimetry (automated threshold testing or Goldmann) is required for the diagnosis and subsequent monitoring of the visual field. Decreased visual acuity early in the course is an ominous prognostic sign and requires prompt treatment.

A unilateral or bilateral abducens nerve palsy may be present [12]. Other ocular motor deficits, such as oculomotor nerve palsy, trochlear nerve palsy, and generalized ophthalmoparesis, are uncommon [13].

Diagnosis

Neuroimaging is necessary in any patient with suspected increased intracranial pressure. Although computed tomography is acceptable in the acute setting to exclude hydrocephalus, hemorrhage, or mass effect, MRI is

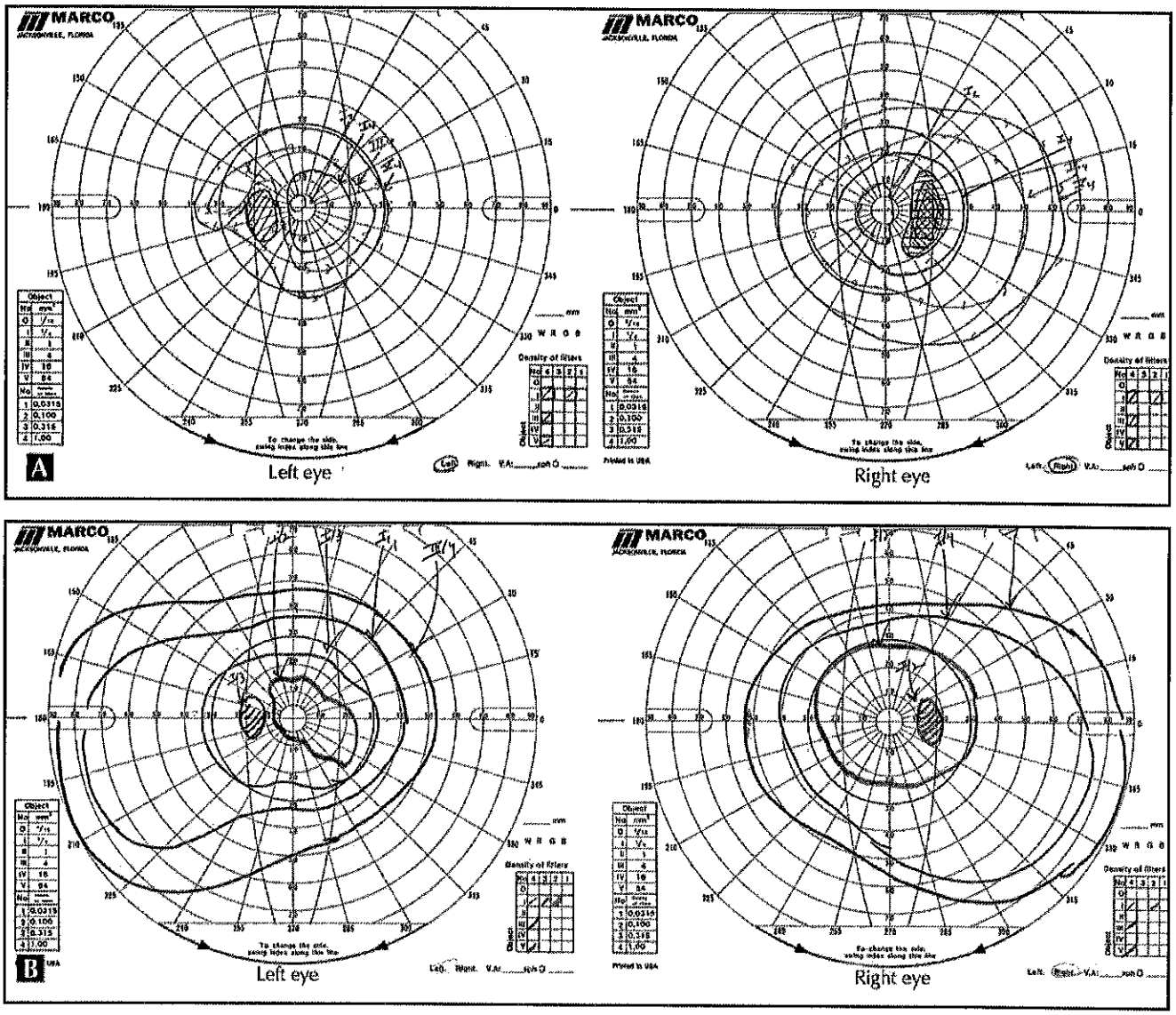

Figure 2. Visual fields at initial examination of the patient in Figure 1. **A**, Moderate constriction with marked blind spot enlargement in the right eye. Marked constriction of the visual field with an enlarged blind spot in the left eye. **B**, Resolution of the visual field defects occurred in both eyes 2 weeks later.

preferred because of its superior resolution and multiplanar capabilities. The sagittal sections often reveal a partially or completely empty sella, indicative of increased intracranial pressure. A Chiari I malformation or cerebellar ectopia may be present [14•]. The ventricles should be normal in size [15]. Orbital images, although not required for the diagnosis, often yield helpful clues, such as flattening of the posterior sclera (producing shortened axial globe length), optic nerve tortuosity, distention of the optic nerve sheath, and protrusion of the optic papillae into the vitreous (Fig. 3) [16,17•]. The role of routine magnetic resonance venography (MRV) is undefined. Cerebral venous sinus thrombosis is a cause of intracranial hypertension and is identified noninvasively using a high-quality MRV. MRV is definitely recommended for "atypical" cases of IIH occurring in men, prepubertal children, women taking oral contraceptives, patients aged older than 45 years at presentation, slim individuals, and patients not responding to treatment. Its utility in "typical" IIH patients (obese women of childbearing age) without known risk factors for venous thrombosis is less certain. Recent studies using auto-triggered, elliptic-centric-ordered, three-dimensional, gadolinium-enhanced (ATECO) MRV demonstrate intraluminal defects, extraluminal compression, and discontinuities of the cerebral veins in patients with IIH [18]. The superior resolution of the ATECO technique offers advantages over time-of-flight MRV, which often shows artifactual changes in the venous system. Smooth-walled stenosis of the transverse sinuses is the most frequent finding in IIH and seems to be a result of increased intracranial pressure rather than the cause of it in most cases [19]. Beyond complete venous thrombosis, the significance of the MRV abnormalities described with IIH is uncertain.

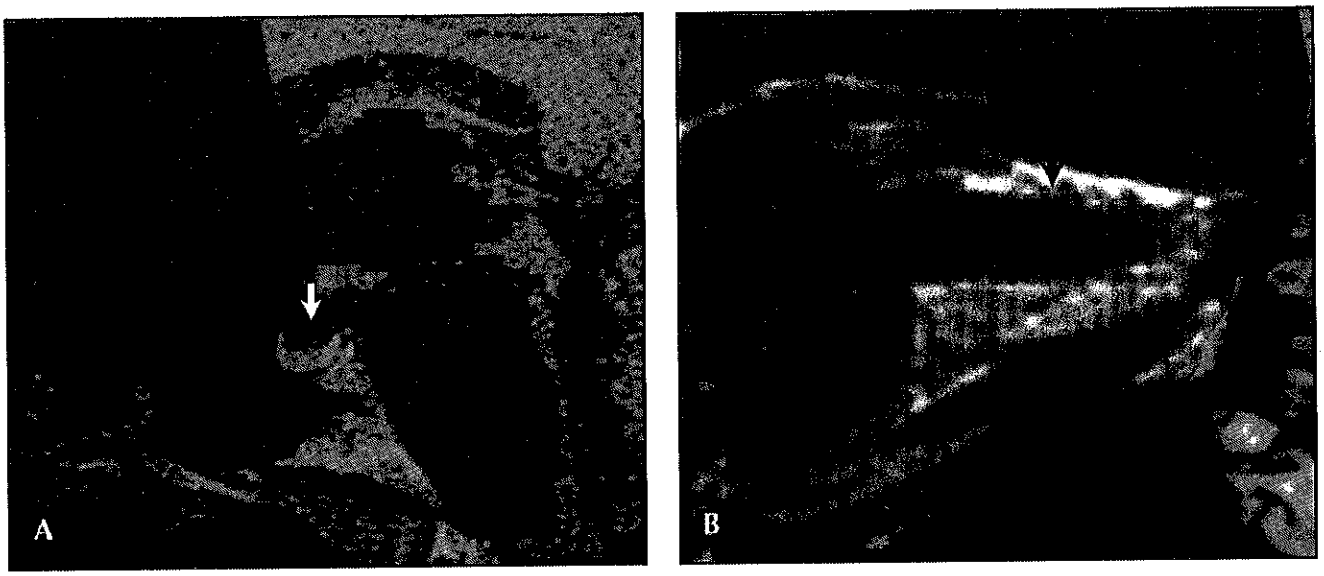

Figure 3. MRI of the patient in Figure 1. **A,** A partially empty sella (*arrow*). **B,** The sagittal view of the orbit reveals distention of the optic nerve sheath (*arrow*), flattening of the posterior sclera, and protrusion of the optic nerve papilla into the globe.

A lumbar puncture is required for the diagnosis. The opening pressure, measured in the lateral decubitus position, should be at least 250 mm of water with normal CSF contents. Normal values for CSF pressure are not established in young children, but intracranial hypertension is suspected with pressures greater than 100 mm of water for children aged younger than 8 years, and greater than 200 mm of water for children aged between 8 and 12 years. If the procedure is initiated with the patient in the sitting position, or performed under fluoroscopy, the patient must be moved to the lateral decubitus position to obtain an accurate pressure reading. The CSF protein is normal or low, and routine studies (including cytology) are recommended on the diagnostic lumbar puncture to exclude hemorrhage, acute or chronic meningitis, inflammation, or malignancy. Physiologic fluctuations in intracranial pressure or inaccurate spinal needle placement may result in a misleading low or normal reading during the lumbar puncture. A Valsalva maneuver may spuriously increase pressure by 150 mm CSF or more [20••]. Repeated pressure measurements may be necessary. The symptomatic response to CSF drainage is not diagnostic, and post–lumbar puncture headaches may occur.

Treatment

Treatment recommendations for IIH are largely based on retrospective studies, case series, and collective experience. Both medical and surgical treatments are used, depending on the patient's symptoms and visual function. The main goal of treatment is to preserve vision, and treatment decisions are primarily based on the patient's visual function. All patients with IIH should be comanaged by a neurologist and an ophthalmologist to monitor their visual status, perimetry, and papilledema grade.

Medical treatment

Weight loss is encouraged for obese patients. The evidence supporting weight loss as an effective treatment is largely retrospective and suggests that losing approximately 6% of body weight is associated with an improvement in papilledema grade [21]. The effect of weight loss on headache and the other associated symptoms of IIH has not been studied, nor has any particular dietary protocol. Because many women with IIH have systemic fluid retention, a low-salt diet that avoids excessive fluid intake may be helpful [22]. In general, weight loss is considered a long-term therapy for IIH and is not useful in the setting of acute visual loss. The role of bariatric surgery is controversial; it may be useful for improving the general health of morbidly obese patients but does not guarantee relief of IIH symptoms. Proponents of bariatric surgery postulate that its effectiveness is related to decreasing intra-abdominal pressure [23], but this proposed mechanism has no physiologic basis [24].

All medications used to treat IIH are considered "off label." Diuretics are routinely used in the treatment of IIH, although there are no randomized trials showing their effectiveness. Acetazolamide, a carbonic anhydrase inhibitor, is used as a first-line therapy to decrease CSF secretion from the choroid plexus. Dosages of 1 to 2 g daily are usually used in adults [25]. Higher dosages, up to 4 g daily, may be used as tolerated. Common side effects of acetazolamide include paresthesias, drowsiness, and altered taste sensation (especially for carbonated beverages). Low serum bicarbonate levels are expected and do not generally require treatment. Severe adverse reactions include allergy, Stevens-Johnson syndrome, aplastic anemia, and renal stones. Aplastic anemia is idiosyncratic and not predictable by routinely monitoring the blood count. Methazolamide, also a carbonic anhydrase inhibitor, is an alternative to acetazolamide. If carbonic anhydrase

inhibitors are not successful, furosemide or other diuretics may be used. Triamterene or spironolactone may be used for patients who are allergic to carbonic anhydrase inhibitors and furosemide.

Headaches from IIH are variably responsive to diuretics but are managed medically. Medications for headache prevention are useful, such as topirimate, tricyclic antidepressants, verapamil, and valproate. Because weight gain may exacerbate IIH, the patient's weight should be monitored carefully during treatment. Symptomatic treatment with migraine-specific medications may be useful, but the use of daily analgesics should be avoided to prevent medication overuse headache. Patients with IIH commonly continue to experience headaches after their intracranial pressure is successfully treated [26].

In general, corticosteroid use should be avoided in IIH patients because the intracranial pressure may increase as dose is tapered, and because of weight gain [27]. Corticosteroids may be useful in the setting of acute visual loss to control the intracranial pressure before a surgical procedure. However, some experts think that corticosteroids may be detrimental in this setting.

Surgical treatment

Surgery is used when patients have significant visual loss at presentation (based on visual acuity or visual field) and when they continue to worsen despite maximum medical treatment. Surgery is not advocated for the treatment of headache alone. The most commonly used treatments are optic nerve sheath fenestration and shunting. Neither procedure has been prospectively studied, and there are no studies directly comparing the two procedures. The decision to use one or the other is often based on the local expertise available. Some patients may require both procedures if one surgical modality fails [28].

Optic nerve sheath fenestration is performed by an experienced orbital surgeon. Papilledema must be present to consider this therapeutic option. Unilateral (on the most affected eye) or bilateral procedures may be performed using either a medial or lateral orbital approach. The surgeon places several fenestrations, or excises a window, along the optic nerve sheath. The mechanism underlying the effectiveness of the procedure is uncertain. There is immediate lowering of CSF pressure in the subarachnoid space surrounding the optic nerve as fluid is released through the fenestration. Once the fenestration heals, the optic nerve may be protected from trabeculations of scar tissue between the optic nerve sheath and the optic nerve, or from a filtering mechanism. Papilledema usually improves after optic nerve sheath fenestration. Approximately 75% of eyes have improvement in the visual field, 65% of patients have improvement in their headaches, and 50% experience improved vision in the unoperated eye [29,30]. The procedure is similarly effective in children [31]. The complications are generally minor and transient, including diplopia, ocular discomfort, and tonic pupil. Visual loss resulting from the surgery occurs in less than 10% of patients, probably caused by ischemia [32]. Failure with recurrent visual loss may occur months to years later. The major advantages of the procedure are the lack of hardware, short duration of the procedure, and amenability to outpatient surgery.

Various types of shunts are used to treat IIH. Proponents of shunting over optic nerve sheath decompression surgery emphasize that it "treats the underlying problem" of increased intracranial pressure. The preference for lumboperitoneal or ventriculoperitoneal shunts has fluctuated over the years. According to a national hospital admission database, the number of shunt procedures for IIH increased by 350% from 1998 to 2002, with new shunt placements increasing by 320% [33]. Shunting almost always works initially, but shunts frequently fail. Visual loss may be the first evidence of shunt failure [34]. Lumboperitoneal shunts are most commonly used for IIH. Their disadvantages include overdrainage with an acquired Chiari malformation or low-pressure headaches, radiculopathy, and a high incidence of shunt failure. A retrospective review of 27 IIH patients treated with lumboperitoneal shunt with a mean follow-up of 6 years showed that 56% of patients required revision. The average revision rate was 2.4 per patient, with a median time to first revision of 11 months. The most common reasons for shunt revision were shunt failure and low CSF pressure [35]. Another study reviewing CSF diversion procedures in 37 patients (73 lumboperitoneal and nine ventricular shunts) showed an average time to shunt failure of 9 months (range from 1 day to > 15 years) [36].

Review of a 30-year experience with shunting for IIH at Johns Hopkins School of Medicine studied 115 shunt procedures (79 lumboperitoneal and 36 ventriculoperitoneal or ventriculoatrial) in 42 patients [37]. Forty-five percent of patients had one procedure, 24% underwent two, 19% underwent three to five procedures, and 12% had six or more procedures. Although 95% had a significant improvement in headaches 1 month after the procedure, headaches recurred in 48% of patients by 36 months. Lumboperitoneal shunts were more likely to require revision (86%) than were ventricular shunts (44%). Overdrainage and tonsillar herniation only occurred with lumboperitoneal shunts, which were twice as likely as ventricular shunts to become obstructed. Ventricular shunts placed with frameless stereotactic guidance were all successfully placed, but 75% failed by 24 months post-insertion. In this series, lack of papilledema and symptoms lasting longer than 2 years were risk factors for treatment failure. Ventriculoperitoneal shunts have the advantage of incorporating programmable valves, although their utility in IIH has not been confirmed.

Secondary Causes of Intracranial Hypertension

The diagnosis of IIH requires the exclusion of a secondary cause. Many secondary causes have been reported in the

literature, but the only case-control study of IIH identified only obesity and a recent weight gain as risk factors [38]. Obstruction to cerebral venous drainage, such as septic or aseptic cerebral venous thrombosis, jugular vein obstruction, and superior vena cava syndrome, may produce a similar syndrome to IIH. Among the many exogenous agents associated with intracranial hypertension, the best evidence exists for the tetracyclines, vitamin A and retinoids, corticosteroid withdrawal, human growth hormone, nalidixic acid, leuprorelin acetate, chlordecone pesticide, and levonorgestrel contraceptive system. After discontinuing the agent, the intracranial pressure does not always revert to normal right away, and other therapeutic measures may be needed in the interim. Intracranial hypertension may occur in the antiphospholipid antibody syndrome, Behçet's disease, polycystic ovarian syndrome, obstructive sleep apnea syndrome, HIV infection, and Turner syndrome. (For a thorough review of secondary causes, refer to the article by Digre and Corbett [39].) There is no confirmed association of IIH with oral contraceptive usage or during pregnancy [40].

Special Circumstances

Pregnancy

Although it may develop or recur during pregnancy, pregnancy is not contraindicated in women with IIH [40]. Most pregnant women may be medically managed using acetazolamide and intermittent lumbar punctures. If necessary, surgery may be performed. Because the expanding uterus may interfere with the shunt catheter, optic nerve sheath fenestration may be preferred to surgically treat visual decline. Corticosteroids also may be used. Medical treatment options are limited; sodium valproate is contraindicated.

Children

IIH may occur at any age. Before puberty it affects boys and girls equally, and obesity is present less often than in adults [41]. Among adolescents, girls are affected more frequently than boys. IIH in young children may present with somnolence, a stiff neck, apathy, ataxia, irritability, or torticollis [42]. A secondary cause is frequently found, such as infection, medication, or otitis media [43]. Management of IIH in children is similar to treatment of adults. Pubertal children may have a less favorable visual prognosis than prepubertal children, teenagers, or adults [44•]. Papilledema is occasionally discovered in asymptomatic children during a routine eye examination [45]. After excluding a tumor or another secondary cause, these children may be followed conservatively if their visual function is normal.

Fulminant IIH

In some cases, the manifestations of IIH appear rapidly with early visual loss. Such patients generally have marked visual field loss or decreased central visual acuity at presentation. There may be marked papilledema, evidence of optic nerve ischemia, and macular edema. These patients require aggressive management, and the physician should use medical and surgical treatments as quickly as possible. However, the visual outcome may be poor despite rapid intervention.

Conclusions

The incidence of IIH in the United States is increasing, requiring a high level of suspicion by medical practitioners. The evaluation of patients with a new onset of headaches, particularly if they are obese women or using medications known to be associated with intracranial hypertension, should include an ophthalmologic examination. Once diagnosed, treatment is initiated and continued based on the patient's visual function and headache disability. Monitoring of vision, headaches, and medical status requires a team approach that is generally coordinated by a neurologist. Although the visual prognosis is generally good, permanent loss of vision may occur.

Acknowledgments

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